UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/976,566	11/24/97	POTTER	A 9001-0016.01

HM32/1215

REED & ROBINS
635 BRYANT STREET
PALO ALTO CA 94301

EXAMINER	
SHAVER, J	
ART UNIT	**PAPER NUMBER**
1641	8

DATE MAILED: 12/15/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

Responsive to communication(s) filed on Election 10/20/98.

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- [x] Claim(s) 37-43 is/are pending in the application.
  - Of the above, claim(s) 38, 39, 42, & 43 is/are withdrawn from consideration.
- [ ] Claim(s) _____ is/are allowed.
- [x] Claim(s) 37, 40 & 41 is/are rejected.
- [ ] Claim(s) _____ is/are objected to.
- [ ] Claims _____ are subject to restriction or election requirement.

Application Papers

- [ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.
- [ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.
- [ ] The specification is objected to by the Examiner.
- [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

- [ ] All [ ] Some* [ ] None of the CERTIFIED copies of the priority documents have been
  - [ ] received.
  - [ ] received in Application No. (Series Code/Serial Number) _____.
  - [ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- [ ] Notice of Reference Cited, PTO-892
- [x] Information Disclosure Statement(s), PTO-1449, Paper No(s). 2
- [ ] Interview Summary, PTO-413
- [x] Notice of Draftsperson's Patent Drawing Review, PTO-948
- [ ] Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

DETAILED ACTION

Sequence Disclosure

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the reasons set forth on the attached Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

APPLICANT MUST COMPLY WITH THE SEQUENCE RULES WITHIN THE SAME TIME PERIOD AS IS GIVEN FOR RESPONSE TO THIS ACTION, 37 C.F.R. 1.821-25. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Applicant is requested to return a copy of the attached Notice to Comply with the response. As this is a divisional application, Applicants may submit a letter stating that the CRF listing for the parent application is the same as for the present case.

NOTE: The claims, specification and drawings should be amended to include specific references to the sequence identification numbers.

Election/Restriction

2. Applicant's election of Species B, chimeric proteins coupled to GnRH, in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 38, 39, 42 and 43 have been withdrawn from further consideration as they are drawn to a non-elected Species.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 37, 40 and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 6, and 9 of U.S. Patent No. 5,422,110. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US Patent No. 5,422,110 recite an "immunological carrier system"; however, said carrier system comprises a leukotoxin fused to a selected antigen which reads on the chimeric proteins of the present invention. Claim 5 of US Patent 5,422,110 specifically recites

leukotoxin polypeptide fused to GnRH. Although the claims are not identically worded it would have been obvious that the chimeric proteins of the present application could be considered immunological carrier systems.

5. Claims 37, 40 and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No.5,837,268. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US Patent No.5,837,268 recite a chimeric protein comprising a leukotoxin polypeptide fused to GnRH. Although US Patent 5,837,268 recites the fusing the leukotoxin polypeptide to specific multimers it still reads on the chimeric proteins of the present invention.

6. Claims 37, 40 and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 19-22 of U.S. Patent No.5,723,129. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of US Patent No.5,723,129 recite chimeric proteins comprising a leukotoxin polypeptide fused to GnRH. Although US Patent 5,723,129 recites the fusing the leukotoxin polypeptide to specific multimers having more than one GnRH polypeptide, the word "comprising" in the instant claims allow for more than one GnRH as well.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and

> exact terms as to enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate as failing to provide an enabling disclosure and failing to provide an adequate written description.

Applicants specification makes broad reference to the preparation of a chimeric protein comprising any antigen and the leukotoxin, wherein certain cytokines have been exemplified as antigens at page 4. The term "antigen" encompasses many different and diverse proteins. However, this very broad common variable/descriptive does not make the preparation and use of one predictable from the other, especially in view of their diverse physical properties. Because of their different physical and functional characteristics, and because of the differences exhibited by their DNA or genes (many of which have multiple forms), the disclose enablement for three antigens (i.e., SRIF, GnRH, and VP4) is not considered sufficient to enable the breadth of any selected antigen. It would therefore require undue experimentation to prepare the vast number of fusion proteins that comprise these antigens, with assurances that they possess the desired activity-particular for use.

Applicant's specification also only exemplifies and enables the preparation of chimeric proteins wherein the cytotoxin is the leukotoxin from *Pasteurella haemolytica*. At the time of the invention it was known that other different leukotoxins existed, i.e., from *Actinobacillus*

actinmycetemcomitans. In view of the fact that these latter leukotoxins are physically and functionally distinct from those disclosed by Applicants, it is suggested that the claims be amended to specifically refer to the leukotoxin from *P. haemolytica*, as the intended use recited by applicant is consistent with use of the *P. haemolytic* leukotoxin. Applicants have inserted the term "RTX" cytotoxin by way of a CIP applicant; however applicants are not enabled, or were not in earlier applications, for leukotoxins other than those from *P. haemolytica*. "RTX" relates generally to gram-negative bacterium which secrete high molecular weight calcium-dependent cytotoxic proteins which includes the cytotoxins of the instant invention. However, applicants are only enabled for use of RTX leukotoxins from *P.haemolytica*, as the term "RTX" encompasses proteins applicants had not identified at the time the invention was made.

Additionally, the specification is only enabled for proteins wherein the entire "full length" sequence of the leukotoxin protein is fused to the cytokine. The specification fail to teach proteins wherein specific epitopes of the leukotoxin are fused to antigens as there is insufficient guidance for the determination and selection of appropriate regions of the protein that would represent epitopes that could be fused to the antigens. There is no evidence of record for the number and regions where epitopes on the leukotoxin protein would occur, other than the description of a consensus sequence where it is speculated that this region is an epitope. The number of epitopes on most proteins vary considerably and in view of the large size of the protein (95 kD), it would require undue experimentation for one skilled in the art to determine the number of epitopes on this protein and subsequently fuse them to a antigen, absent some guidance

or direction for the determination of such. The specification does not provide any guidance for the selection and determination of such region, and such epitopic regions do not appear to be known. Therefore, the specification appears to only be enabling for fusion proteins comprising the entire full length of the cytokines and the leukotoxin.

8. Claim 37, 40 and 41 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

10. Claim 37 is rejected under 35 U.S.C. 102(e) as being anticipated by Potter (5,476,657).

Potter is entitled to a filing date more than one year prior to the effective filing date of the present case.

Potter discloses that leukotoxin from *P.haemolytica* may be used in compositions and vaccines (col. 3, lines 15-25). He also teaches that the disclosed *P.haemolytica* polypeptides, including the leukotoxin polypeptide, may be linked to a carrier which include proteins, fragments and analogs, particularly VP6 of rotavirus (col. 13, lines 9-49).

11. Claim 37 is rejected under 35 U.S.C. 102(e) as being anticipated by Potter (5,238,823).

Potter is entitled to a filing date more than one year prior to the effective filing date of the present case.

Potter et al. disclose the expression of a fusion protein comprising leukotoxin having substantially the sequence of leukotoxin fused to IL-2 (a selected antigen) for use as a vaccine against shipping fever pneumoniae (see Fig. 2 for the plasmid encoding the fusion protein, example 2 for the expression of the protein as well as example 4 for the method of administration of the vaccine in a carrier to calves).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

13. Claims 37 is rejected under 35 U.S.C. § 103 as being unpatentable over any one of Lorberboum-Galski et al, Williams et al, Murphy, or Bell et al ('233 or '711) in view of Highlander et al, Strathdee et al, or Lo et al further in view of Prickett.

Each of the primary references disclose the recombinant production of chimeric proteins (also referred to as hybrid protein, fusion proteins, or conjugates) which comprise a cytokine and various different cytokines. Lorberboum-Galski et al specifically disclose a recombinant chimeric protein between IL-2 and Pseudomonas exotoxin (see pages 1922-24). Further disclosed is that various other toxins have been fused/linked to other proteins. The chimeric protein of Williams et al comprises IL-2 and diphtheria toxin (see pages 493-495). Murphy specifically teaches that hybrid proteins can be prepared comprising various cell specific polypeptide ligands, particularly those that contain binding domains for receptor recognition which are conjugated to diphtheria toxin. Il-2 as well as other cytokines are disclosed (col. 3-4). The '233 patent, Bell et al, specifically claims fusion of Beta IFN-gamma IFN; whereas the '711 Bell et al patent specifically claims gammaIFN-Lymphotoxin. None of these primary references discloses a chimeric protein wherein leukotoxin is the specific cytotoxin for the other fusion partner in the chimeric construct.

Each of the secondary references disclose the cloning of the gene for the leukotoxin from *P.haemolytica* and the DNA/amino acid sequences. Neither of these references teaches the fusion of the leukotoxin to other structural protein. Prickett disclose immunogenic conjugates comprising small peptide regions of leukotoxins and pharmaceutically acceptable carriers or

diluents and/or an adjuvant for the use of inducing an immune response against bovine diseases; specifically against shipping fever (see entire patent).

No one prior art reference individually discloses each aspect of the inventive concept; however at the time the invention was made it would have been prima facie obvious and one would have been motivated to substitute the amino acid sequence for the leukotoxin of any one of the secondary references in place of the sequence of the other cytotoxins in the chimeric protein of any one of the primary references in order to obtain a chimeric protein comprising IL-2 or gamma IFN (selected antigens) with leukotoxin for the ultimate use in treating shipping fever. It would have been further obvious to use only short immunogenic/antigenic regions of the leukotoxin instead of the full length cytotoxin, because Prickett had specifically taught that certain immunogenic peptides from leukotoxin could induce an immune response for effective treatment of bovine diseases. In view of the fact that at the time the invention was made it was well known that many different protein combinations could be prepared recombinantly that produce chimeric protein and because it has also been well established that various cytotoxins have been conjugated to such things as antibodies, ligands, or hormones, to act as site-specific delivery agents (some of which also display functional activity of the cytotoxin), one desirous of treating shipping fever would have found it obvious to use the techniques of the primary reference and construct a chimeric protein comprising IL-2 and/or IFN and the leukotoxin of the secondary reference with the expectation of obtaining a chimeric protein that would be useful to treat shipping fever or other animal infections. One would be further motivated to use IL-2 because it has been shown to

be effective against shipping fever. The selection of the appropriate epitopic sequence on the leukotoxin is obvious from the teaching of Prickett in which immunogenic/antigenic peptide regions on the leukotoxin have been identified and used in a manner as disclosed.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1641 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM. *Please note that the name of the Examiner of record has changed from Jennifer Shaver to Jennifer Graser.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12/14/98

James C. Housel

JAMES C. HOUSEL 12/15/98
SUPERVISORY PATENT EXAMINER